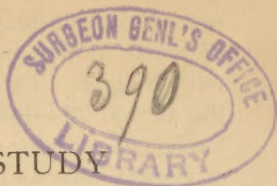


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PHYSIOLOGICAL STUDY  
OF  
**CHLORALAMID.**

**The New Hypnotic.**

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Special Contribution for *NOTES ON NEW REMEDIES*.\*

When chloralamid is given hypodermically in doses of from two to five centigrammes to frogs weighing twenty-five to forty grammes it produces, without any previous evidences of irritation, a profound sluggishness, which deepens in the course of fifteen or twenty minutes to a complete general muscular relaxation, so that the animal remains in any position in which it is placed. There is also progressive slowing of the respiration, and finally complete arrest of the function at a time when the heart is still actively beating. It is probable that the muscular relaxation and the intense general apathy are cerebral, i. e., are the result of stupor, since at a time when the animal lies as though dead, pinching or other peripheral irritation produces movements which are seemingly reflex.

When given to dogs in toxic doses, chloralamid causes sleep, passing into stupor, contracted pupils, primarily increased respiration, great muscular relaxation, and finally death, which appears usually to take place through failure of the respiration. Thus, five grammes of the drug were given by the stomach to a dog weighing five and five-tenths kilos; eleven min-

\* It is due the authors to state that the material for this paper was compiled in November and December of last year, and that the complete MS. was received for publication in February. The importance of this contribution was recognized and early publication seemed desirable, but owing to various circumstances, prior arrangements to fill the limited space at command, and other valid reasons earlier publication was impracticable. We owe an apology to the authors, therefore, for unintentionally risking their claims to priority in this research.—EDITOR.

utes later there was great unsteadiness of gait, with marked incoördination of movement. Before the giving of the drug the pulse was ninety, and the respiration twenty-eight. Twenty minutes after the administration the animal laid down and seemed unable to get up, and had a pulse of one hundred and twenty and a breathing of eighty. Shortly after this there was free vomiting, followed almost immediately by profound sleep. Half an hour after taking the drug the corneal reflexes were distinctly lessened, the respiration fifty-six, and the pulse one hundred and six. One hour after the administration there was a condition of profound narcosis, the pupils were contracted, and the corneal reflexes completely abolished. Death occurred in six hours after the dose was taken.

In another dog, weighing six and three-tenths kilos, three grammes given by the stomach caused in twenty minutes pronounced muscular weakness, with apathy and a doubling of the rate of respiration. One hour after taking the drug the dog was profoundly narcotized, with contracted pupils, abolished corneal reflexes, and slight mucous diarrhoea. During the next half hour there was some return of consciousness and repeated rather severe diarrhoea. Shortly afterward, however, the narcosis came on again, and continued for over one hour. After a sleep of about five hours this dog awoke and finally recovered.

We have not attempted to determine the fatal dose per kilo of chloralamid to the dog, but have found that the dose of two decigrammes per kilo, given by the stomach, produces no very distinct influence. The dose of three decigrammes, however, per kilo, caused some drowsiness without actual sleep, and in some instances was followed by pronounced diarrhoea.

Chloralamid exercises a very distinct power in lowering the bodily temperature. Thus in an experiment in which a large dose was followed by profound stupor, ending, however, in recovery, the rectal temperature in the course of a few hours fell from  $39.1^{\circ}$  C. to  $36^{\circ}$  C., and in another dog to which a fatal dose was given, the rectal temperature fell from  $36.06^{\circ}$  C. to  $29.1^{\circ}$  C. just before death.

The most marked symptom produced by chloralamid in our experiments upon the dog was stupor, with hurried respiration; but as showing in detail the changes in the respiration, and blood pressure, and pulse, we append the following experiments, the one made with a small and the other with a very large dose. We also give a photographic reproduction of a tracing to show that during complete narcotism there may be no pronounced reduction of respiration or circulation.



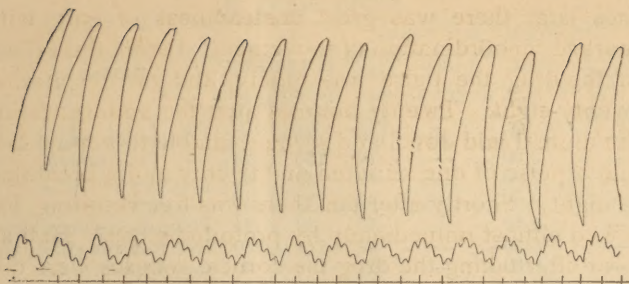


Fig. A 1.

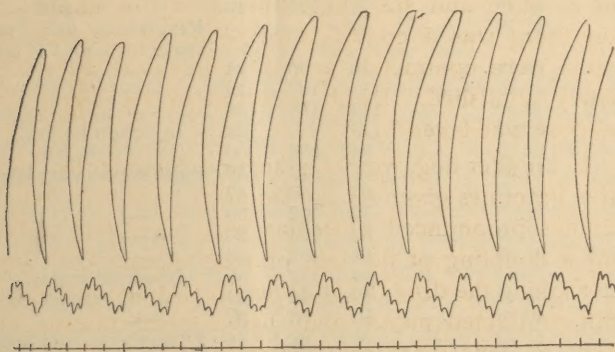


Fig. A 2.

Tracing No. 1: taken upon dog in normal state.

Tracing No. 2: taken when the dog was thoroughly narcotized, having had one and a half grammes of chloralamid by intravenous injection.

## EXPERIMENT I.

Dog-Wght: 14.059 Kilos.

RECT. TEMP.	TIME	DOSE	PRESSURE	PULSE	RESP.	REMARKS.
Co.	h. m. s.	grammes.	mm.	p. min.	p. min.	
39.03	0.	—	110	198	24	—
—	.40	1	110	198	24	Injection begun.
—	1.10	—	110	198	24	“ ended.
—	1.30	1	100	210	30	“ begun.
—	1.40	—	100	210	30	“ ended.
—	2.	1	90	210	30	“ begun.
—	2.20	—	90	192	24	“ ended.
—	4.20	—	90	186	150	—
—	8.20	—	90	114	168	—
39.03	10.50	—	100	102	204	Pulse waves large.
—	11.50	—	100	102	216	—
—	15.30	—	100	108	240	—
—	20.30	—	100	120	240	Animal narcotized; eye reflexes almost gone.
39.01	24.20	—	100	120	240	—
—	26.	—	100	108	240	—
—	28.40	2	96	114	240	Injection begun.
—	29.20	—	80	126	222	“ ended.
—	33.20	—	100	138	198	—
38.09	38.20	—	100	138	198	—
—	43.20	—	100	132	210	—
—	48.	5	104	156	186	Injection begun.
—	49.30	—	80	144	78	“ ended.
—	50.30	—	96	156	24	—
—	53.20	—	100	156	36	—
38.08	59.	—	100	156	96	—
—	1. 3.30	5	100	156	108	Injection begun.
—	1. 5.10	—	76	138	84	“ ended.
—	1. 5.50	—	90	144	60	—
—	1.10.20	5	100	162	66	Injection begun.
—	1.11.50	—	70	120	54	“ ended.
38.05	1.15.10	—	70	120	54	—
—	1.18.10	—	—	—	—	Animal died from respiratory failure; heart stopped in diastole and remained irritable.

## EXPERIMENT II.

Dog-Wght: 32.6 Kilos.

RECT. TEMP.	TIME	DOSE	PRESS- URE	PULSE	RESP.	REMARKS
Co.	h. m. s.	grammes.	mm.	p. min.	p. min.	
40.02	0.	—	150	156	18	—
—	.40	10	150	156	18	Injection begun.
—	2.20	—	70	156	24	" ended.
—	2.50	—	20	42	42	—
—	3.50	—	50	84	18	—
—	4.50	—	70	80	24	Pulse waves very large.
—	5.50	—	80	114	30	Eye reflexes gone; ani-
—	8.50	—	100	156	30	mal hypnotized.
—	11.	—	110	180	54	—
—	14.30	10	120	168	42	Injection begun.
—	16.10	—	70	120	48	" ended.
—	17.10	—	—	—	—	Respiration and heart cease for about ½ min.
—	19.10	—	70	96	24	—
—	20.40	—	110	168	30	—
40.02	22.40	—	110	180	36	—
—	23.20	6	110	210	54	Injection begun.
—	24.20	—	90	168	60	" ended.
—	25.20	—	50	72	36	Pulse waves very large.
—	26.20	—	60	96	42	" " " "
—	31.50	—	70	102	30	—
—	32.50	—	80	156	30	—
40.02	38.20	—	84	180	48	—
—	38.50	4	84	174	36	Injection begun.
—	39.50	—	50	96	30	" ended.
—	40.40	—	50	66	30	—
—	41.40	—	50	90	24	Pulse waves very large.
—	46.40	—	50	96	30	Cut both Vagi.
—	47.10	—	50	102	24	—
—	47.50	—	50	96	30	Animal killed with eth- er about 1 min. after.

In attempting to draw more definite conclusions as to the physiological action of chloralamid, for the sake of clearness and brevity, it is best to separately study its influence on different portions of the organism.

*Nervous System.*—The early development of stupor, and the fact that the animal lies in a profound sleep, relaxed and unconscious, at a time when reflex movements are readily produced by peripheral irritation, shows that the chloralamid exerts a powerful influence upon the cerebrum. The persistence of the reflexes until very late in the narcosis indicates that the effect of the poison upon the lower nervous apparatus is subordinate to its cerebral action, but in a series of experiments upon pithed frogs it was found that very large doses distinctly decreased the activity of the reflexes; in no instance was any stage of primary increase of sensitiveness perceived. The depression was due to an action upon the spinal cord, as was demonstrated by finding that a feeble galvanic current of fixed strength caused contractions when applied to the nerves, but produced no effect when passed through the spinal cord. This was confirmed by the experiments made with tying the abdominal aorta; an examination of the example given below will show that such tying had no influence upon the development of paralysis, so that we must conclude that chloralamid is a *feeble spinal depressant*.

Pithed two frogs of equal size, and tied abdominal aorta of one. Waited for shock to pass off:

TIME h. m.	Reflex action in operated frog.	Reflex action in normal frog.
3.45	in 10 seconds	in 12 seconds
3.50	" 10 "	" 12 "
4.	" 10 "	" 12 "
4.10	Injected 0.05 centigr.	Injected 0.05 centigr.
4.20	Reflex act. in 15 seconds.	Reflex act. in 15 seconds.
4.30	" " " 15 "	" " " 16 "
4.35	" " " 20 "	" " " 18 "
4.45	" " " 25 "	" " " 25 "
4.55	" " " 30 "	" " " 30 "
5.10	" " " 32 "	" " " 33 "
5.30	" " " 1 minute.	" " " 1 min. 3 sec.
5.45	No action in 1.30. Died subsequently.—After death.	No action in 1.30.

*Respiration.*—The action of chloralamid upon the respiration is very pronounced. By looking back it will be seen that in the experiment I. three grammes increased the respiration about ten fold, that is, from twenty-four to two hundred and forty per minute; this increase persisting through the long period of narcosis, but followed, when a large and fatal dose of the drug was injected, by a distinct fall of rate, which was not however sufficient to bring the respiration to the normal rapidity. Even just before the final arrest, which occurred suddenly, the respiratory movements were still rapid. Sudden arrest of respiration has seemed to be the rule in our experiments. The following photographic reproduction of a tracing shows how the circulation continues after suppiratory arrest:

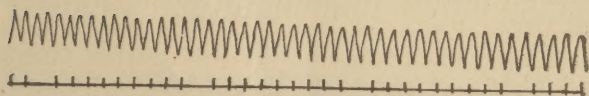
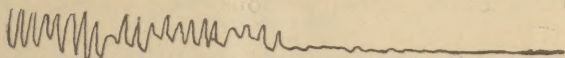


Fig. F.

We have not made any experiments absolutely measuring the amount of air passed through the lungs, but

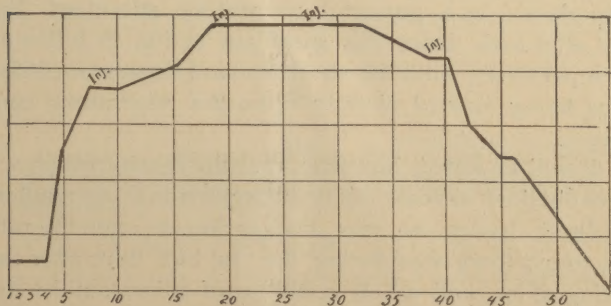


Fig. B.

Fig. B. A curve showing graphically the effect of injection of a narcotic dose of chloralamid upon the respiration rate in a dog whose vagi had been previously cut.



have used a respiratory tambour so fixed as to work with regularity, usually the increase was only one of rate, but in some of our experiments the excursions of the tambour needle showed that not merely the rate, but also the size of the respiratory movements were increased: see tracing A and also a plotted curve B.

The action of chloralamid upon the respiration seems to be a centric one. Thus, in a dog in which both vagi had been cut, and the slow full respirations were steady at twelve per minute, the injection into the jugular vein of five grammes of chloralamid was followed in one minute by a stupendous rise in the number of respirations per minute; in two minutes the rate was two hundred and sixty-four, in four minutes two hundred and eighty-two, and in seven minutes two hundred and ninety-four per minute. Under the administration of more of the remedy the respiration rose to three hundred a minute, or twenty-five times the rate which it had been before the chloralamid had been injected: as shown in accompany of tracing.

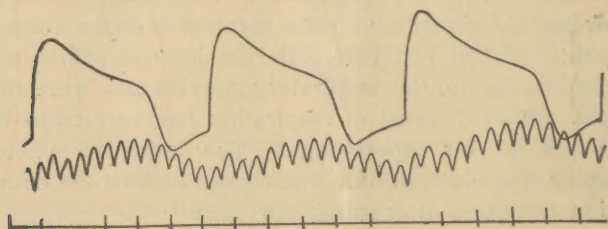


Fig. C1.

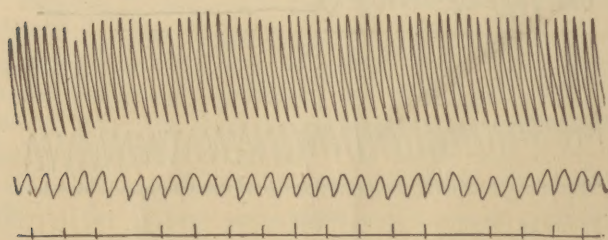


Fig. C2.

It would appear, therefore, from our researches, that chloralamid is a powerful respiratory stimulant, but that after toxic doses this stimulant action is followed by a paralysis; both the stimulant and depressant influence being exerted directly upon the respiratory centres.

It will be noted, however, that the results which we have obtained are essentially different from those reached by Dr. A. LANGGAARD, who, in experiments upon the rabbit, found there was during the first half hour after the taking of one and a half grammes of chloralamid a decrease of nineteen per cent., in the second half hour thirty-seven per cent. in the air drawn in and out of the lungs. VON MERING and ZUNTZ have, however, shown

that when the rabbit goes to sleep there is a natural falling off of more than thirty per cent. in the activity of the respiration; so that the decrease in the breathing of LANGGAARD's rabbit was not more than the norm. Our experiments have been made upon the dogs, but we are at a loss to account for the difference in results, unless by supposing that in LANGGAARD's experiments the chloralamid was absorbed so slowly and in such small amounts as to have little influence upon the respiratory centre. At one time we thought it possible that our samples of chloralamid might possibly contain free ammonia, but careful chemical testing disproved this idea. In all our dogs death took place through *paralysis of the respiration*, the *heart continuing to beat actively long after the arrest of breathing*: as illustrating the comparative effects of the drug upon respiration and circulation we append the following photographic representation of a tracing:

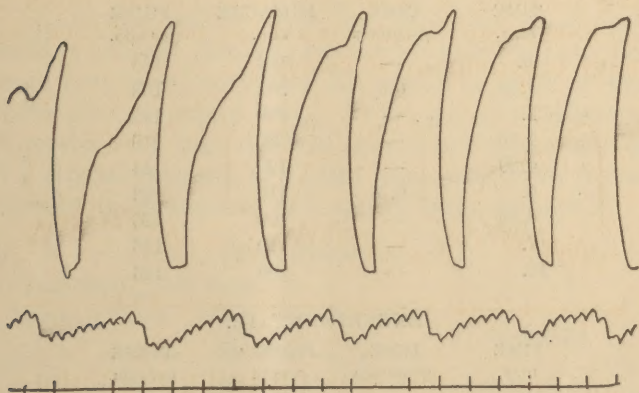


Fig. D 1.

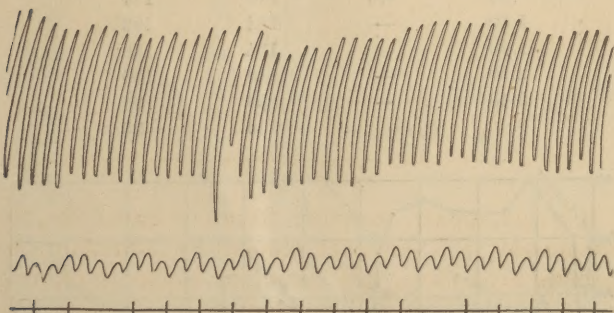


Fig. D 2.

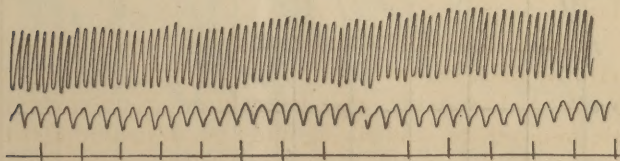


Fig. D 3.

Fig. D shows the effect upon the respiration and circulation of the intravenous injection of a full narcotic

dose of chloralamid. D 1, before the injection; D 2, immediately after the development of narcosis; D 3, ten minutes later.

*Circulation.*—The action of chloralamid upon the blood pressure is much less marked than its influence upon the nervous system.

The reference to experiments 1 and 2 will show that the blood pressure is primarily reduced; the fact that when the chloralamid is thrown into the jugular vein there is an immediate excessive fall, (see experiment 2,) followed by recovery, indicates that the drug has a direct depressing influence upon the heart itself.

There is reason for believing that very small doses of chloralamid have a stimulating influence upon the circulation, as is shown in the following experiments:

#### EXPERIMENT III.

TIME m. s.	DOSE grammes	PRESSURE mm.	PULSE per min.
0.	—	104	168
.30	0.5	104	168
1.	—	108	192
1.30	—	90	216
4.30	—	120	144
6.	0.5	110	102
6.30	—	100	126
7.	—	110	126
10.	--	100	126

#### EXPERIMENT IV.

TIME m. s.	DOSE grammes	PRESSURE mm.	PULSE per min.
0.	—	140	114
.50	0.5	140	114
1.10	—	132	102
1.40	—	114	156
2.10	—	140	186
5.10	—	160	96
8.	—	150	96

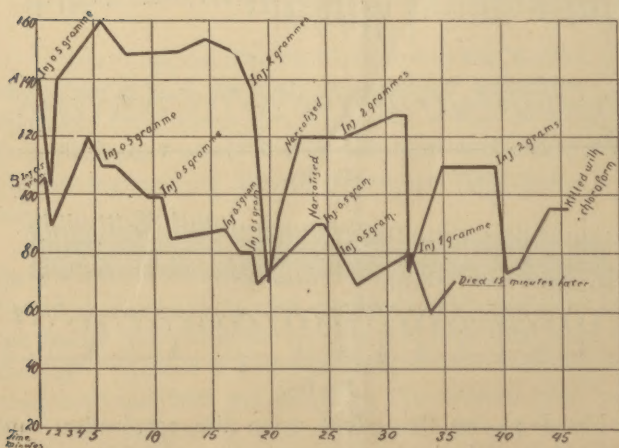


Fig. E1.



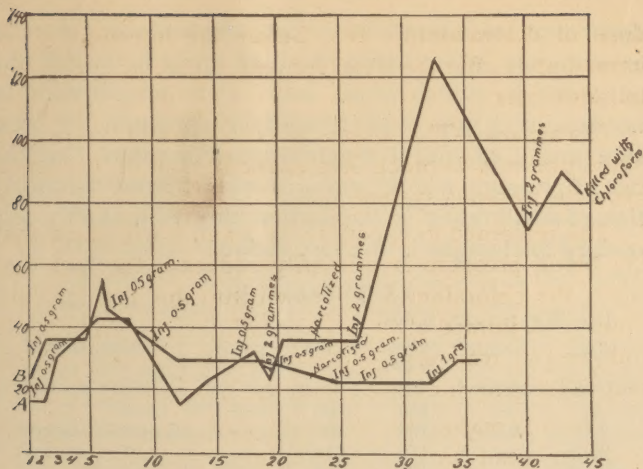


Fig. E2.

Curves showing effects of chloralamid injections on blood pressure in normal animals. Bottom figures = time in minutes. Side figures = height in mm.

As already stated, when the large dose of chloralamid is injected directly into the torrent of the circulation, there is an immediate fall, which is more or less thoroughly recovered from. Under any circumstances, however, very large doses of chloralamid finally reduce the arterial pressure, and after toxic doses this fall of pressure is pronounced as is shown in experiment V.

## EXPERIMENT V.

Dog-Wght: 7.256 Kilos.

TIME	DOSE	PRESS.	PULSE	RESP.	REMARKS.
h. m. s.	grammes.	mm.	per min.	per min.	
0	—	106	132	—	—
.30	2	106	132	—	Injection begun.
1.20	—	60	126	—	" ended.
2.20	—	80	150	—	—
3.20	—	80	162	—	—
8.50	—	84	126	—	—
13.50	—	84	120	—	—
18.50	2	84	96	—	Injection begun.
19.40	—	80	108	—	" ended.
21.40	—	100	150	—	—
24.40	—	96	162	—	—
40.—	2	110	168	—	Injection begun.
40.40	—	92	156	—	" ended.
42.—	—	90	144	—	—
44.40	—	100	144	—	—
49.40	4	96	156	—	Injection begun.
50.30	—	60	114	—	" ended.
51.30	—	68	114	—	Pulse waves large.
52.20	—	80	120	—	—
55.20	—	110	144	—	—
1. 0.20	—	110	144	—	—
1. 5.20	—	110	144	—	—
1.10.20	—	110	144	—	—
1.15.20	5	100	180	—	Injection begun.
1.16.20	—	60	102	—	" ended.
1.17.20	—	20	24	—	Pulse waves very large.
1.18.20	—	10	42	—	—
1.19.20	—	—	—	—	Animal dead.

Our next experiments were made upon curarized animals to determine whether the changes in the circulation, which have just been spoken of, were in-

dependent of alterations in the respirations. Several experiments were made, but we give in detail the only one in which small doses were employed. In no case was any even temporary elevation of pressure produced, and it would appear therefore that the rise of pressure which we have seen follow the injection of small doses in the normal dog is probably secondary to changes in the respiration.

## EXPERIMENT VI.

Dog-Wght: 6.009 Kilos.

TIME	DOSE	PRESS- URE	PULSE.	RESP.	REMARKS.
h. m. s.	grammes.	mm.	per min.	per min.	Animal Curarized.
0.	—	160	120	—	—
20.	0.5	160	120	—	Injection begun.
20.50	—	116	114	—	“ ended.
21.30	—	124	114	—	—
22.	—	132	126	—	—
24.30	—	130	132	—	—
27.30	—	136	138	—	—
29.30	—	130	138	—	—
32.40	0.5	130	138	—	Injection begun.
33.40	—	112	114	—	“ ended.
34.30	—	124	138	—	—
37.30	—	130	150	—	—
42.30	—	130	150	—	—
47.30	—	120	144	—	—
52.30	—	120	138	—	—
57.30	—	100	120	—	—

In order to determine whether the fall of the blood pressure is due to an action upon the vaso-motor system or upon the heart, experiments were made upon dogs in which the cord and the vagi had been divided before the administration of the drug. These experiments are as follows:

## EXPERIMENT VII. (Cord and vagi cut.)

Dog-Wght: 6.575 Kilos.

TIME	DOSE	PRESS- URE	PULSE	RESP.	REMARKS.
m. s.	grammes.	mm.	per min.	per min.	
0.	—	40	120	—	—
.40	2	40	120	—	Injection begun.
1.30	—	30	96	—	“ ended.
2.30	—	20	90	—	—
3.40	—	16	84	—	—
5.10	—	16	84	—	—
10.10	—	16	84	—	Pulse waves very large.
15.10	—	16	84	—	—
18.10	—	20	84	—	—
27.30	2	20	84	—	Injection begun.
28.10	—	10	66	—	“ ended.
29.10	—	6	66	—	—
29.20	—	—	—	—	Animal dead.

## EXPERIMENT VIII. (Cord and vagi cut.)

Dog-Wght: 7.029 Kilos.

TIME	DOSE	PRESS- URE	PULSE	RESP.	REMARKS.
m. s.	grammes.	mm.	per min.	per min.	
0.	—	20	138	—	—
.40	2	20	138	—	Injection begun.
1.20	—	20	108	—	“ ended.
1.40	—	10	105	—	—
2.	—	—	—	—	Animal dead.

These two experiments show that division of the cord does not prevent immediate fall of pressure, pro-



duced by injection of chloralamid, and we therefore conclude that the drug has a depressing influence upon the heart.

*Conclusions.*—Our researches have been made solely upon dogs, and therefore the following conclusions apply directly to those animals.

*First.* Chloralamid has a slight local influence, and in large doses tends to produce mucous diarrhoea.

*Second.* It acts more powerfully upon the cerebral cortex than upon any other portion of the nervous system of voluntary life, thereby causing sleep and muscular relaxation; but it is also a feeble spinal depressant.

*Third.* It has a powerful influence upon the respiration, in moderate dose, by a centric action stimulating the respiratory rate, and probably also increasing the actual amount of air breathed; but in toxic dose causing death by paralysis.

*Fourth.* Its influence upon the circulation is a very feeble one; the changes produced by small doses being probably secondary to other effects of the drug; toxic doses, however, depress the arterial pressure by a direct action either upon the heart or upon the muscle coats in the arterioles.

#### THERAPEUTICALLY CONSIDERED.

The results of our experiments indicate that chloralamid is very worthy of trial as a hypnotic. Its action upon the heart is so slight that it bids fair to be valuable as a hypnotic in cases of feeble heart; whilst its stimulating influence upon the respiration would seem to fit it for employment in cases of nervous exhaustion. The exact clinical value of a hypnotic can, however, only be determined by clinical study. Dr. H. C. Wood has used the remedy to a moderate extent in various forms of insomnia, and so far it has seemed to him to be slower and less certain in its action than is chloral. Rarely have unpleasant after-effects been noted, but he has seen in some cases distinct headache. The statement of HAGEN and HÜFLER that the drug is especially valuable in cardiac asthma seems to be consonant with our experimental conclusions.

Laboratory of Experimental Therapeutics,  
University of Pennsylvania.

February 20, 1891.



